Remarks

Please cancel claims 4, 7-8 and 14-15 without prejudice to renewal.

Claims 1, 9 and 16 are amended herein. Claims 1, 9 and 16 are amended to correct form. Claims 1 and 9 are also amended to remove reference to nucleic acids encoding a VP22 protein coupled to a functionally active amino acid sequence.

Applicants reserve the right to pursue the canceled subject matter in a continuation application. No new matter is added.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-6, 9-13 and 16 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly the specification does not provide enablement for the *in vivo* use of nucleic acids encoding the VP22 fusion protein.

With regard to claim 1, and claims that depend therefrom, Applicants respectfully disagree with this assertion. The Office action states that the specification is enabling for the *in vitro* and the *in vivo* use of the VP22 fusion protein.[1] Thus, solely to advance prosecution, and not for reasons pertaining to patentability, claim 1 is amended herein to be directed solely to the fusion proteins themselves (and not to nucleic acids encoding the fusion proteins). Applicants retain the right to pursue this subject matter in a continuation application.

Claim 9 (and claims that depend therefrom) are not directed to nucleic acids encoding the fusion protein, but are directed to methods of reducing the proliferation of cells using the fusion proteins. Thus, Applicants respectfully submit that this rejection is not applicable. Applicants request, therefore, that the rejection of claim 9 and dependent claim 16 be withdrawn.

Thus, Applicants submit that claims 1-6, 9-13 and 16 are fully enabled by the specification. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-6 and 9-10 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over O'Hare et al. (WO 98/32866) in view of Dilber et al., *Gene Therapy* 6:12 (1999) and the subject specification (at page 3, lines 14-28 and page 8, lines 1-10). Claims 11-13 and 16 were

also rejected under 35 U.S.C. § 103(a) as allegedly being obvious over O'Hare et al. in view of Dilber et al. and the subject specification. Applicants respectfully disagree with these rejections.

O'Hare et al. teaches proteins which can be coupled to VP22, such as p53. O'Hare et al. further discloses that fusion protein can be produced that include a VP22 protein and a protein that affects cell cycle control or suicide proteins. However, O'Hare does not teach or suggest the use of polypeptides including the transport function of VP22 coupled to a polypeptide that regulates the progression of the cell cycle in combination with an agent that further stimulates cell death to further reduce the proliferation of cells.

Dilber et al. discloses the use of VP22 protein coupled to HSV-thymidine kinase (TK) protein, along with the prodrug, ganciclovir (GCV), to induce cell death. The HSV-TK is required to phosphorylate GCV to yield a toxic metabolite, monophosphorylated-GCV. Dilber et al. describes that the administration of fusion protein including VP22 and a specific enzyme with a prodrug can result in a toxic bystander effect in cancer cells.

In the experiments described by Dilber et al., GCV itself is not a cell-killing agent; it must be administered in combination with HSV TK. Thus, Dilber et al. does not use, nor does it suggest administration of a cell killing agent. The application provides examples of these agents that stimulate cell death directly: drugs which themselves can induce cell cycle arrest (page 4, lines 20-21), chemotherapeutics (page 5, lines 1-3), DNA damaging agents (page 5 lines 10-12), agents that increase a cell's susceptibility to DNA damage (page 5 lines 16-21) or cytotoxic radiation. These agents are not prodrugs.

The description in the application of the prior art found in the specification describes that VP22-fusion proteins were known in the art. In addition, the application provides examples of proteins that can regulate cell cycle progression (see page 3, lines 14-29 and on page 4 lines 1-13). However, the application does not propose that the prior art can be construed to suggest the claimed methods.

The legal standard applicable to determinations under 35 U.S.C. § 103 based on a combination of references was reiterated by the Court of Appeals for the Federal Circuit in *In Re Dow Chemical Co.*, 837 F.2d 469, 472-473, 5 USPQ2d 1529,1531 (Fed. Cir. 1888):

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[1] See the Office action at page 2. The Office action further states that the specification is enabled for the *in vitro* use of nucleic acids encoding the VP22 fusion protein.

> The consistent criterion for the determination of obviousness is whether the prior art would suggest to one of ordinary skill in the art that this process [i.e. the process of the invention] shall be carried out and would have a reasonable expectation of success, viewed in the light of the prior art. Both the suggestion and the expectation of the success must be found in the prior art, not in the applicant's disclosure [emphasis added, citation omitted].

See also *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016,1022; 927 F.2d 1200, 1207 (Fed. Cir. 1991), and MPEP § 2143 and 2143.01.

Three elements must be established by the rejection in order to make a *prima facie* case of obviousness. First, the prior art must suggest, or provide an incentive for the combination of references; second, the combination as suggested or motivated by the art must yield the process or invention claimed; and third, the prior art must provide a reasonable expectation of success of the claimed invention. At no point may the applicant's disclosure be used to satisfy the three elements (see the MPEP 2142). If any of these elements is absent, the rejection based on obviousness is unsupported.

Against this background, Applicant submits that no *prima facie* case of obviousness has been established. One of skill in the art, reading the work of O'Hare et al., on VP22-cell cycle fusion proteins, would not be motivated to combine the use of the VP22-cell cycle fusion proteins with the use of the VP22-HSV-TK proteins disclosed by Dilber et al. and then treat these cells with a prodrug. Furthermore, even if one were to make the impermissible combination, the claimed invention would not result. The prodrug, GCV is not a cell killing agent. GCV is a non-toxic prodrug (Dilber et al., page 15, col. 1, paragraph 2). Administered alone, it has no cytotoxic effect on tumor cells *in vitro* (Dilber et al., see Fig. 4) and exerts neither a regression nor enhancing effect on tumor growth *in vivo* (Dilber et al., page 8, col. 1, paragraph 2). Thus, even if one were to administer a VP22 fusion-cell cycle fusion protein with a VP22-HSV-TK fusion protein, and treat the cells with the non-toxic prodrug GCV, it would not be obvious to further administer an agent that directly stimulates cell death.

For these reasons, Applicants respectfully submit O'Hare and/or Dilber et al. and/or the citations of prior art in the specification, whether taken alone or in combination, do not render

the pending claims obvious. Reconsideration and withdrawal of the rejection in respect of these claims are respectfully requested.

Conclusion

Applicants submit that the pending claims are now in condition for allowance. If any minor matters remain to be addressed before a Notice of Allowance is issued, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

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